Reply to the Letter: Improving the Safety of ALPPS Procedure: The Optimal Compromise Between the Optimal Compromise Between Drop-out and Mortality Risk? Comment on: Schadde E et al Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg. 2015;262: 780-786.

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Reply to the Letter: Improving the Safety of ALPPS Procedure: The Optimal Compromise Between Drop-out and Mortality Risk? Comment on: Schadde E et al Prediction of Mortality After ALPPS Stage-1: An Analysis of 320 Patients From the International ALPPS Registry. Ann Surg. 2015;262:780–786

To the Editor:

We thank Drs Viganò, Cimino, Adam, and Torzilli for their interest on our analysis of the ALPPS registry and their critical points.[1]

The authors challenge the proposed criteria to delay the second stage of ALPPS (completion hepatectomy) in presence of an Model of End Stage Liver Disease score greater than 10 and positive International Study Group of Liver Surgery criteria.[2] They speculate that applying such criteria may result in a 30% drop-out similar to previous 2-stage hepatectomy. They also suggest differentiating ''oncological'' (tumor progression) versus ''functional (liver failure) drop-out'' claiming that the drop-out in ALPPS is functional, whereas the oncologic drop-out associated with the standard 2-stage hepatectomy is rather oncologic leading to some sort of natural selection.

The main benefit of ALPPS indeed lies in the shortened interstage interval enabling potentially curative resection with a reported drop-out rate of only 2% in colorectal liver metastases.[3] The typical interstage period of 7 to 10 days in ALPPS have to be 4 to 8 times replicated to reach the reported interstage time period of conventional 2-stage hepatectomy.[3] In our experience, prolongation of interstage interval due to liver dysfunction exceptionally exceeds 3 weeks, and therefore still prevents tumor progression in most cases. The advantage is also on the oncologic perspective, because adjuvant chemotherapy cannot be started at an earliest time in other approaches (Kambakamba P, Linecker M, Alvarez, FA, et al. ALPPS reduces chemotherapy-free interval and may improve oncological outcome in patients with bilobar colorectal liver metastases, in preparation.).

We agree, however, that oncological outcome remains one of the hottest topics in ALPPS. There are currently no convincing data on the oncological outcome of ALPPS in comparison with conventional two-stage hepatectomy, and lacking a randomized controlled trial (RCT), we may only speculate on the interpretation on any retrospective comparison. For example, we attempted—with one of the coauthors of your letter (R. Adam)—a case-matched analysis of ALPPS versus standard two-stage hepatectomy using the LiverMetSurvey database and the international ALPPS registry. The retrospective, voluntary, and missing information in both registries prevent definitive conclusion, but only offer a crude evaluation indicating comparable long-term outcome measures between both groups. Therefore, we launched a randomized controlled trial targeting bilateral liver colorectal metastases, which is currently open to the 230 centers registered in the ALPPS registry (www.alpps.net).

We agree with Viganò et al[2] that an age limitation of 60 years is too restrictive considering the worldwide aging population. This cut-off is only indicative of an additional risk factor, but in no way precludes surgery. Of note, the most recent safety analysis of the ALPPS registry, which was presented at the last annual meeting of the ESA, identified an age of 67 as best cut-off for predicting mortality after ALPPS, probably due to the use of safer surgeries compared to the initial cases included.[4] Therefore, the previous recommendation on age must be corrected because almost 25% of patients in this analysis belonged to the age segment of 60 to 67 years, and would be classified with an incorrectly high risk.

The authors further propagate their experience with ultrasound-guided parenchyma-sparing one-stage hepatectomy[5] as an effective alternative to two-stage hepatectomy in bilobar colorectal liver metastases. In our experience, most patients treated with the ALPPS approach would not qualify for any types of ''single'' surgery approach. In addition, the available comparative studies experience major selection bias and heterogeneity of the study population.

In summary, ALPPS is a young procedure still in its development phase with many variants to improve safety.[6] The learning curve is still one of the major determinants of safety; only 10% of the registered centers in the ALPPS registry have performed more than 10 cases and 214 registered centers entered less than 10 cases. Analyses from the international ALPPS Registry remain the best available evidence to study safety and oncological efficacy short of higher-level evidence studies. Therefore, the oncological efficacy of ALPPS remains purely speculative. We agree with the authors that ALPPS is definitively not a procedure applicable for all colorectal liver metastases but is certainly a very useful tool for the experienced HPB surgeon in a variety of complex situations including small future liver remnants in which mono- or bisegment ALPPS are the only option, failure of portal vein embolization, or tumors close to important vascular structures.

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The authors report no conflicts of interest.

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